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GIP-TRIAD Master's Degree in Agro-Biomedical Science

College of Medicine

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Comprehensive report

藥品可及性的跨大陸比較分析

A cross-continental comparative analysis of the drug access system

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摘要

藥品可及性延遲是藥證取得、藥品定價、藥品納入健保延遲所得到的結果，這會對個人的健康和財政狀況造成負面影響。本文利用各國衛生主管機關公開的資料，比較分析北美、歐洲、亞洲等不同大陸間的藥品可及性、新藥申請、藥品定價等過程及系統，並透過 Cyramza (Ramucirumab) 和 Zejula (Niraparib)這兩個藥品的案例分析，來強化論述。此分析總結出藥證取得延遲通常各國相似，但是藥品納入健保卻因為各國投入健保的預算及當地未滿足醫療需求不同，而造成相當大的延遲差異，總體來說，這個比較分析報告提供了不同大陸間製藥產業的法規和定價系統有價值的洞見，以期待能增加藥品可及性。

關鍵字：藥品可及性延遲、藥品定價、藥品納入健保延遲

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Abstract

Drug access delays, including market authorization, pricing, and reimbursement delays, can significantly impact individuals' health and wealth. The study analyzes drug access, new drug approval processes, and pricing systems in several continents, including North America, Europe, and Asia, based on data disclosed by their regulatory authorities. The analysis relies on two case studies (Cyramza (Ramucirumab) and Zejula (Niraparib)) to strengthen the finding. This report finds that the market authorization waiting time is usually similar within countries. However, reimbursement delays can vary significantly because of the healthcare budget and national unmet medical needs differences. Overall, the comparative analysis provides valuable insights into the pharmaceutical industry's regulatory frameworks and pricing mechanisms in different regions, emphasizing the need for ongoing policy development to improve drug access and affordability globally.

Key words: drug access delays, market authorization delays, pricing delays, and reimbursement delays

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Introduction

Drug access delay can negatively impact individuals' health outcomes, leading to disease progression, prolonged recovery time, and even death. Abdelrahman, et al. (2016), a survey on physicians indicated 67 physicians (35%) face patient death due to drug shortage (1). It can also increase the economic burden by expanding the hospitality period and can cause anxiety or other emotional burdens. McLaughlin et al. (2013) shows that complaints were reported by 38% of respondents (24). Pauwels et al. (2015) reports that out-of-pocket cost increased in general medicine: always-often (11%), sometimes (13%), rarely-never (45%), no answer (31%) (29). Combining the disease, financial, and emotional burden may cause a worse quality of life.

Drug access systems can vary significantly from country to country. The system consists of market authorization, drug pricing, and the reimbursement system in each country. In some developed countries that introduced the cost-effectiveness assessment scheme, "market access delay"—the delay between marketing authorization and completion of the reimbursement process for an innovative medicine—has been recognized as a common problem (38).

The study analyzes new drug approval processes, pricing, and reimbursement systems in several continents, including North America, Europe, and Asia. The paper examines how these countries differ regarding regulatory frameworks, new drug

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approval, pricing mechanisms, and access to essential medicines. Only a few papers take Taiwan into drug market access continental analysis, so this is a specialty of this paper. Overall, the comparative analysis provides valuable insights into the pharmaceutical industry's regulatory frameworks in different regions, emphasizing the need for ongoing research and policy development to improve drug access and affordability globally.

A flow chart is made in Figure 1 to summarize the flow of the drug access system.

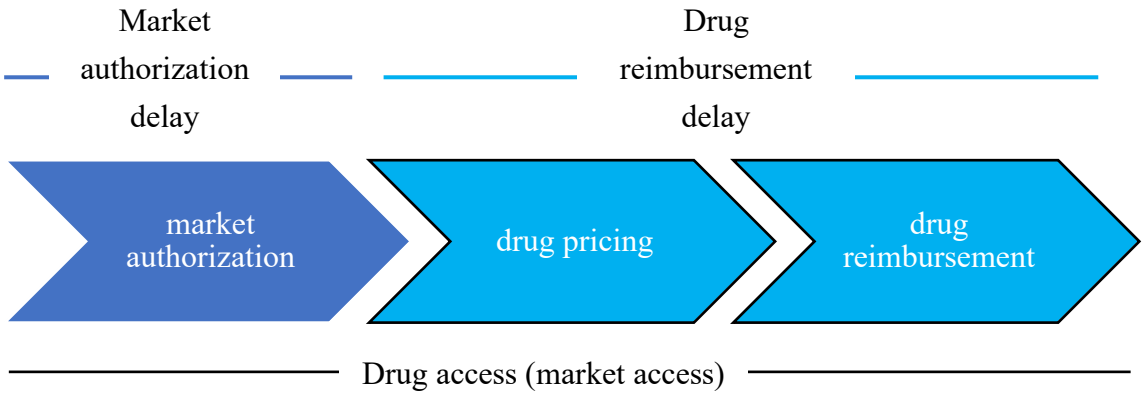

Figure 1. The flow chart of the drug access process.

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Market authorization

Market authorization for a new drug is a crucial step in drug development. It involves a comprehensive evaluation of the safety, efficacy, and quality of a drug by regulatory agencies such as the U.S. Food and Drug Administration (FDA[1]), the European Medicines Agency (EMA[2]), the Pharmaceuticals and Medical Devices Agency (PMDA[3]), and Taiwan Food and Drug Administration (TFDA[4]). The process typically involves several phases of clinical trials, starting with small-scale studies to assess safety and dosing and gradually moving towards larger-scale trials to assess efficacy and safety in the broader population. Once a drug has completed all necessary clinical trials and demonstrated safety and efficacy, the pharmaceutical company can submit a New Drug Application (NDA) to the regulatory authority. The NDA contains detailed information on the drug's development, clinical trial results, manufacturing processes, and any proposed labeling and packaging information. Regulatory authorities then thoroughly review the NDA, including all data submitted by the drug manufacturer. If the regulatory agency confirms that the drug's benefits outweigh its potential risks, it can be granted market authorization, allowing it to be marketed and sold to patients.

[1] https://www.fda.gov/
[2] https://www.ema.europa.eu/en
[3] https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0003.html
[4] https://www.fda.gov.tw/eng/

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The waiting time for market authorization is calculated by measuring the duration between the submission of the NDA and the approval by the respective regulatory authorities in each country. The report includes the drug market authorization time data of the US, the EU, and Japan from 2012 to 2021 from the R&D briefing report published by the Centre for Innovation in Regulatory Science (CIRS[5]) in London, UK, in 2022. In Figure 2, data shows that the new active substance (NAS) median approval time in FDA is the shortest (median: 285.4 days), followed by PMDA(median: 312.3 days), TFDA (median: 328.6 days), and EMA (median: 435.6 days) (30).

FDA is faster than others, which might be because of the following reasons. The agency has more budget and effort on this market because this market is the biggest in the world. There are many big pharmaceutical companies in the United States, leading to high competition in market access approval timing. The FDA received new drug authorization applications median time is 20 (0-98) days earlier than EMA (23). The usage and the number of facilitated regulatory pathways (FRP) in the FDA have increased in recent five years, including «Priority Review»(a evaluation process for the drug proven superior to the standard treatment), «Accelerated Approval»(Regulations permitting the approval of drugs for severe conditions that address an unmet medical need, relying on an alternative endpoint), «Fast Track» (A process developed for

[5] https://www.cirsci.org/

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accelerating the development and evaluation to the drug for severe indication), and «Breakthrough Therapy» (A process developed for accelerating the development and evaluation of drug which is superior to the available treatment) than the other countries. In particular, drugs that undergo priority review can shorten the review time from ten to six months (30).

EMA is responsible for the drug evaluation of centralized market authorization. After receiving the market authorization then, it can be used by the EU members. Moreover, there are some FRPs that facilitate the market authorization in EMA, such as «EMA Accelerated Assessment» (A process created to accelerate the approval of products with significant public health impact and therapeutic innovation), «EMA Conditional Approval» (Regulations allows the approval of drugs with limited clinical safety or efficacy data as long as there is a positive benefit-risk balance), «EMA Exceptional Circumstances»(Regulation permits the approval of drugs for severe, life-threatening, or rare diseases even in the absence of comprehensive efficacy and safety data), and «EMA PRIME» (a program provides support for drug development and evaluation). Notably, for drugs undergoing «EMA Accelerated Assessment», the duration for the Committee for Medicinal Products for Human Use (CHMP) to provide its opinion has been reduced from 210 days into 150 days (30). In some cases, temporary use authorizations (Autorisation Temporaire d'Utilisation, ATU) can help decrease the

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delay, such as in France. ATU is a process for a medicine that does not have an MA and can not provide to patients through a clinical trial (20).

According to Honig et al. (2014), there exists a notable delay in the approval of drugs in Japan compared to the Western regions such as the United States and European Union. This delay can be attributed to several factors, including the limited reviewer capacity within the Japanese regulatory authority and the clinical research infrastructure in Japan. Additionally, the absence of comprehensive clinical and statistical guidelines provided by the PMDA poses challenges for drug developers. While governmental initiatives have aimed to reduce Japan-specific timelines for clinical development and regulatory reviews, the primary reason for the drug lag persists: NDA in Japan are typically submitted later than those in other regions (17). However, there are some FRPs that facilitate market authorization in Japan, which consist of «PMDA Priority Review» (a process to accelerate drug approval for high unmet needs), «PMDA Conditional Early Approval» (A system that accelerate the approval of highly effective drugs for treating severe diseases at the earliest possible stage), and «PMDA Sakigake (pioneer)» (A system designed to accelerate the approval of highly effective drugs for treating severe diseases at the earliest possible stage). In particular, drugs that undergo priority review can shorten the review time from nine to six months (30).

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While South Korea and Taiwan may occasionally request applicants to conduct small-scale bridging studies involving their respective populations for NDA already approved in other countries, Japan stands out as the only Asian country that consistently requires companies to gather clinical trial data based on patient nationality. In contrast, other Asian countries generally accept foreign data alone for drug approval, without the need for nationality-specific clinical trial data. A bridging study is conducted in a new region to gather additional data on efficacy, safety, dosage, and dose regimen in that specific region. This information helps to connect the existing data from the other areas and apply it to the new region (28). Additionally, there are five FRP used in Taiwan, including «Abbreviated Review» (a fast evaluation process for categories I and II drugs, which have already been approved by two of the three regulatory agencies (US FDA, EMA, or MHLW/PMDA)), «Priority Review»(a process to accelerate drug approval for high unmet needs), «Accelerated Approval»(a process to accelerate drug approval for high unmet needs or for drugs that A10 countries have already granted the orphan drug's license), «Breakthrough Therapy»(A process developed for accelerating the development and evaluation of medicine which is superior to the available treatment), and «Pediatric and Rare Severe Disease Priority Review Voucher Program»(a fast drug approval for the disease is mainly prevalent in pediatric population or the prevalence of the disease is less than five per ten thousand). Drugs which undergo Abbreviated

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Review can shorten the review time into 120-180 days. For those which undergo «Priority Review», «Accelerated Approval», «Breakthrough Therapy» and «Pediatric and Rare Severe Disease Priority Review Voucher Program» can shorten the review time to 240 days (5).

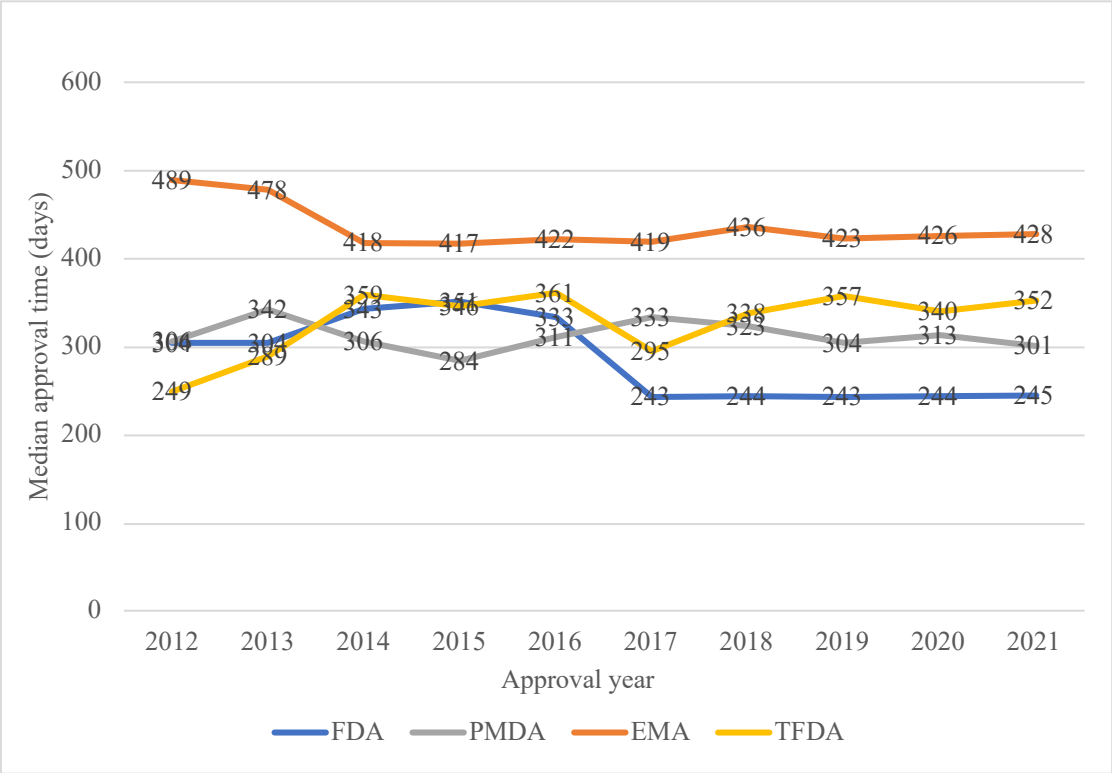

Figure 2. NAS median market authorization approval time in four regulatory authorities in 2012 to 2021 (30).

Additionally, in Figure 2, there is a decrease in approval time from 2017 to 2021 compared to 2012-2016. In Figure 3, the data from the R&D briefing report published by the Centre for Innovation in Regulatory Science (CIRS) located in London, UK, in 2022 were extracted and shows that the usage and the number of FRP have increased in recent five years, except PMDA. The reason for the decreased application through FRP

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in Japan probably is that «Sakigake» requires that the product be a first-in-world regulatory submission. The limited acceptance of English documents presents challenges to developing a unified global dossier. (3) FDA uses FRP the most within all selected agencies accounting for 72% (n=259) of all NDA these five years compared to 60% (n=186) in the previous five years. Therefore, it explains that the approval time drops around 2017 in Figure 2.

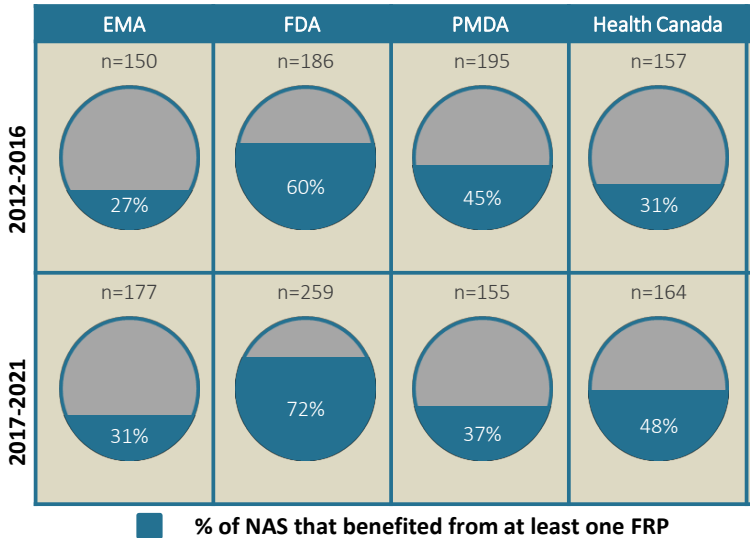

Figure 3. The proportion of NAS under FRP approved by each agency between 2012-2016 vs. 2017-2021 (30).

Drug Pricing

Before the pricing and reimbursement system works, health technology assessment (HTA) should be implemented. It is an assessment to determine Pharmacoeconomics, including the analysis of comparative effectiveness, cost-effectiveness, budget impact, etc. It can increase the pricing and reimbursement decision efficiency (21).

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Drug pricing is a complex issue that involves multiple stakeholders, including pharmaceutical companies, insurance providers, healthcare providers, and governments. In countries with national healthcare systems, the government often plays a significant role in regulating drug prices. The drug pricing process and policy vary in different countries and the specific healthcare system (6,15).

However, the government may use various tools to regulate drug prices, including price negotiation, reference pricing, and cost-sharing arrangements. Price negotiation involves the government negotiating directly with pharmaceutical companies to determine the price of prescription drugs. Sometimes, the government may use its purchasing power to negotiate lower prices for a particular drug or class of drugs. Reference pricing involves setting a maximum price for a particular drug based on the price of similar drugs in other countries or regions. This can effectively control costs but also limit patient access to newer or more expensive drugs (6,15).

The US government does not directly govern drug prices, but it is a part of setting reimbursement rates for prescription drugs through the Medicare program. The government negotiates drug prices for Medicare[6], the federal healthcare insurance for people 65 or older, and some people under 65 with certain disabilities or conditions.

[6] https://www.medicare.gov/

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The government negotiates drug prices for Medicaid[7], the federal-state healthcare program for low-income individuals.

In the EU, there is a different pricing system within each country. Take France as an example in Europe because pricing policy differs in every European country. France has two key markets, including the out-patient market (pharmacy) and the in-patient use market (hospital). The drugs have five ratings, including ASMRI, ASMRII, ASMRIII, ASMRIV, and ASMRV (see Table 1 below). Table 1 is adapted from the data of Vogler, Sabine (2020): PPRI Pharma Brief: France report. Different drug rating needs to follow different pricing rules. The pricing committee is Economic Committee for Health Products (Comité économique des produits de santé, CEPS[8]) following the French law (Article L162-16-4 of the Social Security Code). The price referencing in France is about the price in Spain, German, United Kindom, and Italy. The list of drug prices should be below the lowest price in the reference countries (33).

[7] https://www.medicaid.gov/

[8] https://gnius.esante.gouv.fr/fr/acteurs/fiches-acteur/comite-economique-des-produits-de-sante-ceps

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Table 1. The definition of Authority of Health Scale I-V (ASMRI-V) (33).

Rating of ASMR	Definition
ASMR I	major improvement (new therapeutic area, reduction of mortality
ASMR II	significant improvement in efficacy and/or reduction of side-effects
ASMR III	modest improvement in efficacy and/or reduction of side-effects
ASMR IV	They are priced at the same level of a comparator medicine(s)
ASMR V	below the price of the comparator(s).

In Asia, in terms of Japan, the pricing of drugs and biologicals is governed by the NHI. The Ministry of Health, Labour and Welfare[9] (MHLW) establishes drug pricing dtandards and drug calculation method under the Health Insurance Act. And the price of each drug is announced by the MHLW after consultation with the Central Social Insurance Medical Council. The prices of medicines are periodically investigated by the official market price survey and updated to medical institutions and pharmacies.

Since January 2010, drug applications in Taiwan have been classified into three distinct categories based on the results of clinical trials. Table 2 is adapted from Chen et al. (2018). In Taiwan, the pricing of drugs is determined based on different categories.

[9] https://www.mhlw.go.jp/english/

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Category 1 drugs are priced considering the median price of the A10 reference countries, which include developed nations like the United States, the United Kingdom, Canada, France, Belgium, Germany, Japan, Sweden, Australia, and Switzerland. On the other hand, category 2 drugs (2A and 2B) have their prices lower than the median price of the A10 reference countries. The pricing of category 2 drugs follows specific schemes based on their clinical merits, including factors such as the lowest price among the A10 countries, the international drug price ratio, the treatment-course dosage ratio, and the price in the original country. For combination drugs, the price is determined either as 70% of the sum of each ingredient's price or based on the price of a single active ingredient. (6).

Table 2. Categories of new drug application in Taiwan (6).

category	Definition
Category 1	This evaluation process involves conducting a thorough assessment that includes comparing the new drug directly to the most effective drugs currently available in the market. Additionally, it entails an comparison by referring to published clinical studies in order to identify evidence of the new drug's breakthrough nature and its significant enhancements in clinical effectiveness.

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Category 2A	The new drug is directly compared to the top-performing drugs available in the market. The aim is to gather evidence that demonstrates a moderate improvement in clinical efficacy.
Category 2B	The new drug demonstrates comparable or similar clinical value to the referenced drug listed in the reimbursement scheme.

Reimbursement

In many countries with national healthcare systems, the government plays a significant role in reimbursing patients for the cost of prescription drugs. Reimbursement refers to the process by which the cost of a medication is covered by an insurance provider or government program rather than being paid entirely by the patient (out of pocket). Conversely, the reimbursement payer in the United States is primarily the private sector.

For individuals residing in the United States, Medicare serves as the federal health insurance program for those who are aged 65 or above, as well as certain individuals with disabilities who are younger. Medicare provides the reimbursement of medicine which are on the list. The critical part for the policymaker in reimbursement is to find the balance between patient health outcomes, healthcare policy sustainability, and the impact on the industry. The rest of the people in the United States whom Medicare does not cover must find their own private insurance companies.

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In France, many parties join in the reimbursement decision discussion, including French National Authority for Health (Haute Autorité de santé, HAS[10]), Transparency Committee (CT), Public Health Assessment Committee (Commission Evaluation Economique et de Santé Publique, CEESP[11]), CEPS, and National Union of Health Insurance Funds (Union Nationale des Caisses d'Assurance Maladie, UNCAM) (15, 32).

Pricing and the reimbursement of the drug in France are based on the assessment by French National Authority for Health (HAS) through the opinion from CT and the CEESP (15, 32). CEESP will evaluate the pricing of the drug used in the hospital and pharmacy, and the one which will be out-patient use will be considered by CEPS. The Ministry of Health will announce the final decision of all of them (15, 32). Figure 4 is the flow chart adapted from Rémuzat et al. (2015) summarizing French reimbursement system.

There are five levels of actual benefit (Service Médical Rendu, SMR), including major, important, moderate, weak, and insufficient. They drive the reimbursement rates set by the National Union of Health Insurance Funds (Union Nationale des Caisses d'Assurance Maladie, UNCAM): 100% or 65%, 65%, 30%, 15%, and 0%, respectively (15, 32).

[10] https://www.has-sante.fr/jcms/r_1455134/en/about-has
[11] https://www.has-sante.fr/jcms/c_419565/fr/commission-d-evaluation-economique-et-de-sante-publique

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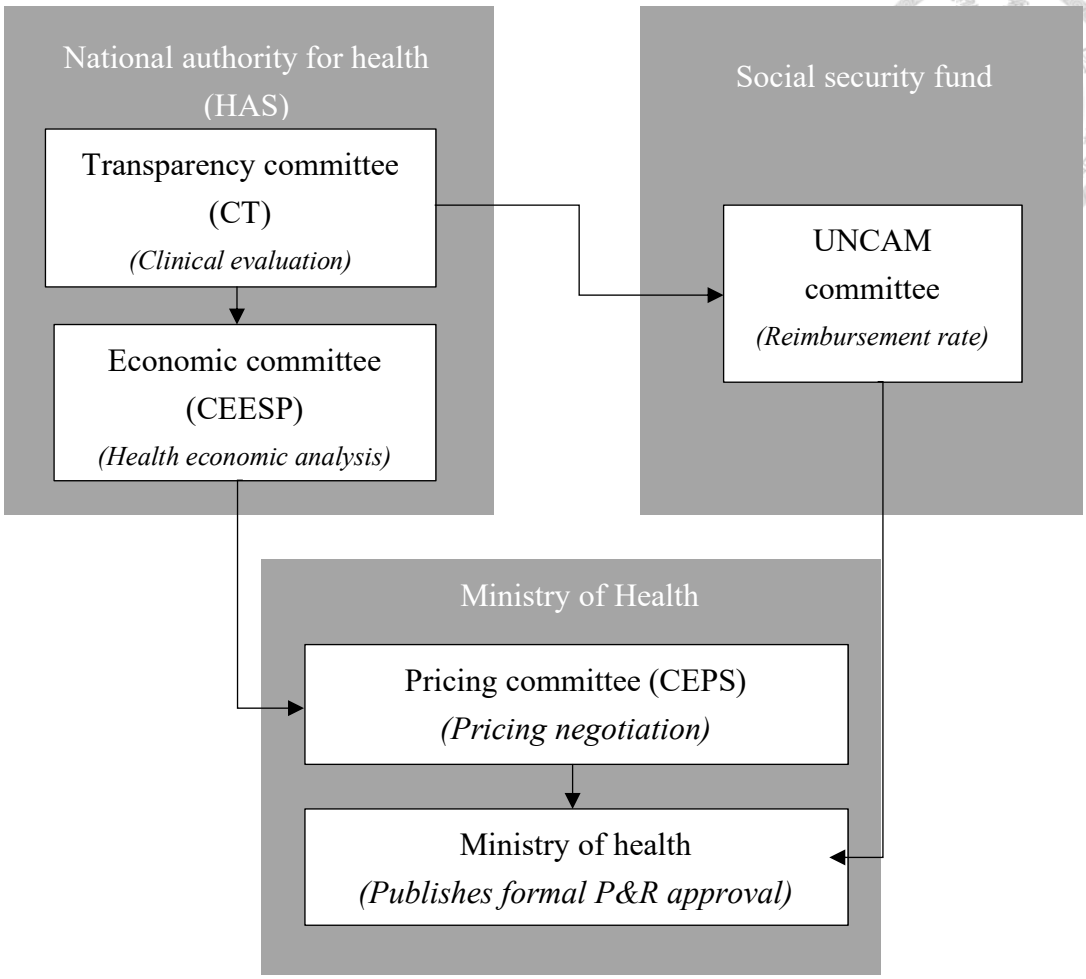

*Figure 4. The flow chart of French reimbursement process (*15, 32*).*

In Asia, we take Japan and Taiwan as examples. In Japan, authorization is governed by Japan's «Pharmaceuticals and Medical Devices Law» (the "PMD Act"). The Health Insurance Act governs reimbursement. MHLW specifies the drugs and their prices that are eligible for coverage under insurance for healthcare. National health insurance (NHI) Drug Price Standard specifies drugs usable in insurance-covered healthcare, and functions as an item list. Figure 5 is the flow chart adapted from PMDA summarizing Japan's reimbursement system. One major different reimbursement system in Japan is that they have the HTA only for pricing, not reimbursement. Also, the pricing and

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reimbursement evaluation were kept in 60-90 days to avoid drug access delay. They list the drugs on the approved and reimbursed list then can evaluate them within 2 years (21).

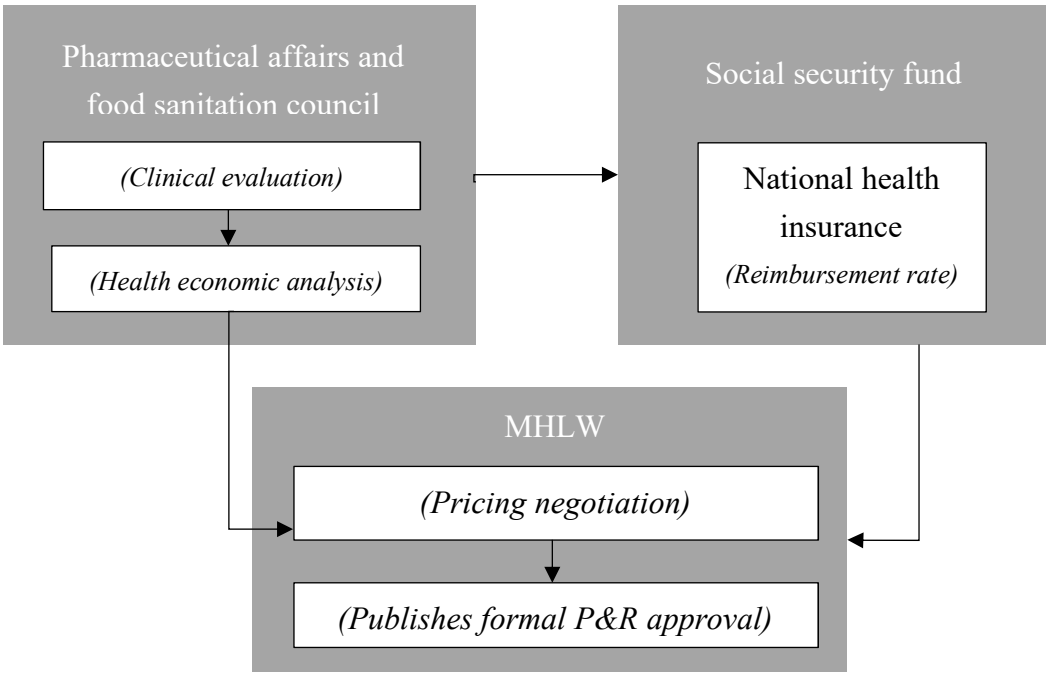

Figure 5. *The flow chart of the reimbursement process in Japan*

In Taiwan, the TFDA plays a crucial role in the assessment and authorization process for new drugs. The Minister of Health and Welfare (MOHW) holds the authority to specify the eligible drugs and their pricing for coverage under healthcare insurance. Subsequently, the National Health Insurance Administration (NHIA) is responsible for determining the reimbursement criteria for newly approved drugs (6).

Figure 6 is the flow chart adapted from Chen et al. (2018) summarizing Taiwan's reimbursement system (6).

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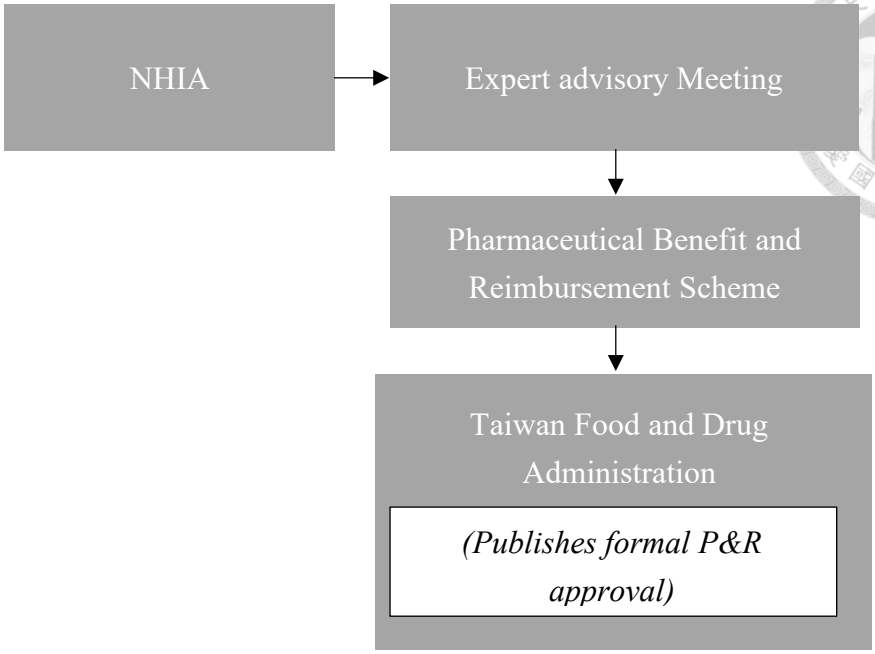

Figure 6. The flow chart of the reimbursement process in Taiwan (6)

Starting from 2007, Taiwan commenced conducting HTA to facilitate decision-making and present clinical effectiveness and economic impacts evidence. From 2007 to 2013, the Drug Benefit Committee (DBC) carried out expert evaluations of NDA, which subsequently led to decisions about listing new drugs. On January 1, 2013, the first generation of Taiwan NHI system changed into the second generation. After this transition, the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) Joint Committee was established for NHI reimbursement. Apart from making reimbursement decisions, the PBRS also determines the final NHI reimbursement price (34).

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By combing the data of reimbursement delay time of Taiwan and Japan from Shih et al. (2020) and the data from the report on Shortening the wait - patient access to medicines in Europe on the EFPIA[12] Homepage, Figure 7 is created.

In the initial generation of Taiwan's National Health Insurance (NHI) system, the average reimbursement delay for new drugs was 378 days (with a range of 128 to 11,070 days). In the second-generation of NHI, this average increased to 458 days (with a range of 274 to 2,189 days). On the other hand, in Japan, the average waiting time between marketing authorization and the release of a drug reimbursement decision was 66 days. The swift reimbursement decisions in Japan may be attributed to the fact that, before April 2016, the Japanese NHI listing system did not require cost-effectiveness evidence. In addition, the MHLW in Japan requires that the process of listing prices for NHI should be finished within 60 days, with 90 days as the maximum, to guarantee that patients can quickly avail of the latest medicines (34). According to the data from EFPIA Patients W.A.I.T. Indicator 2022 Survey, from 2018 to 2021, the mean time of availability (days)in France, Spain, and Italy are 508, 629, and 436, respectively. The availability time is the days between receiving the market authorization and accessing the reimbursement list (36).

[12] https://www.efpia.eu/

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Figure 7 shows the comparison of the reimbursement delay days from the company's reimbursement application until the reimbursed drug price is listed and released in Spain, Italy, France, Japan, and Taiwan. The average waiting days are similar except for Japan. To ensure swift patient access to advanced medications, Japan has implemented a law governing reimbursement. The MHLW in Japan declares that the NHI price listing process should be completed within 60 days to 90 days (34). Conversely, the reimbursement delay in Taiwan can be attributed to factors such as a higher budget impact and the implementation of the second-generation NHI. Specifically, the introduction of the second-generation NHI has notably prolonged the reimbursement lag for new drugs classified under the Anatomical Therapeutic Chemical (ATC) group L, which encompasses antineoplastic and immunomodulating agents according to the World Health Organization classification. Most new ATC group L drugs were rated as moderate improvement (category 2A) and produced by the international pharmaceutical companies; they often suggest high reimbursement rate for these drugs.

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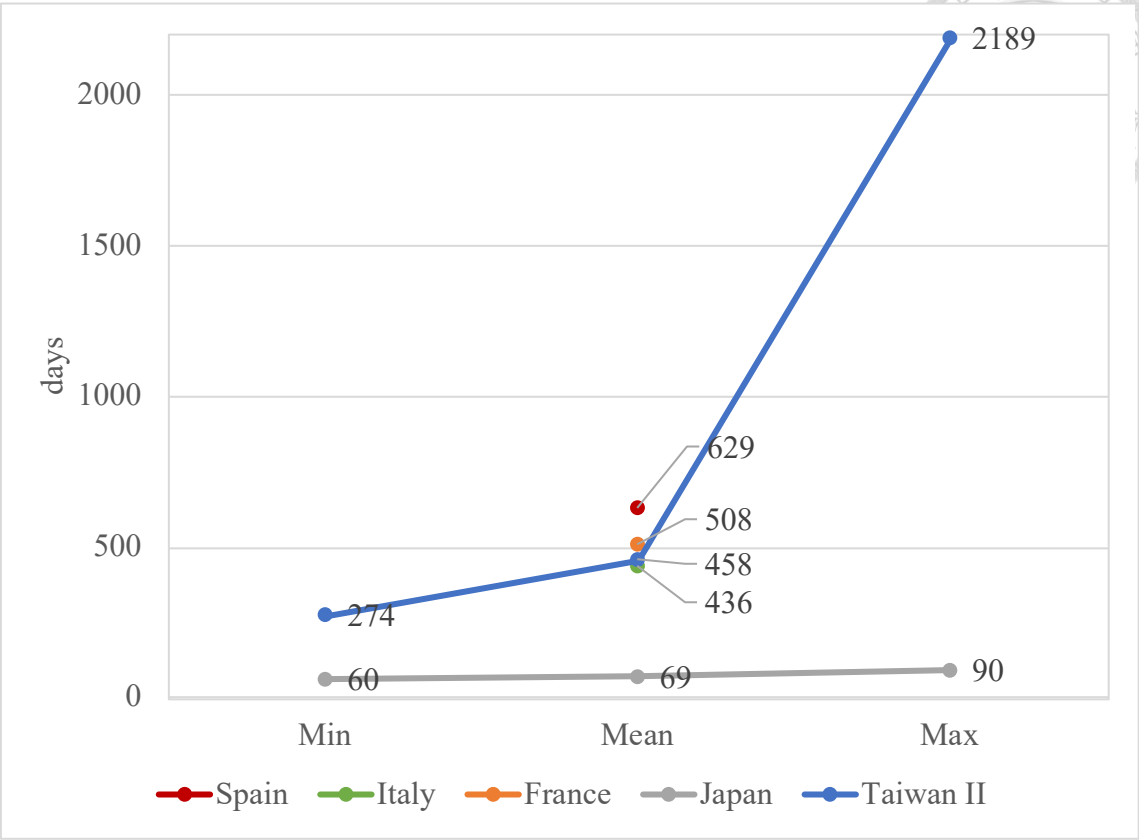

Figure 7. The reimbursement delay days in 3 European countries (France, Italy, and Spain), Japan, and Taiwan II (The second Taiwan National Health second generation) (34, 36).

Current health expenditure includes personal health care (curative care, rehabilitative care, long-term care, ancillary services, and medical goods) and collective services (prevention and public health services and health administration) but excludes investment spending. Current health expenditure spent on healthcare compared to the overall economy shows how important healthcare is and how much society values it. The current health expenditure (CHE) per GDP indicates which country spends more on health care and drug access. Figure 8 combines the CHE/GDP data of the USA, France,

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and Japan from 2012 to 2021 from the OECD[13] and Taiwan's CHE/GDP data from the National health insurance annual statistical report published by the NHIA, Ministry of Health and Welfare to compare their budget in health care. The data shows that the CHE/GDP from 2012 to 2021 is highest in the USA (mean=16.8) and lowest in TW (mean=6) (16, 23, 27).

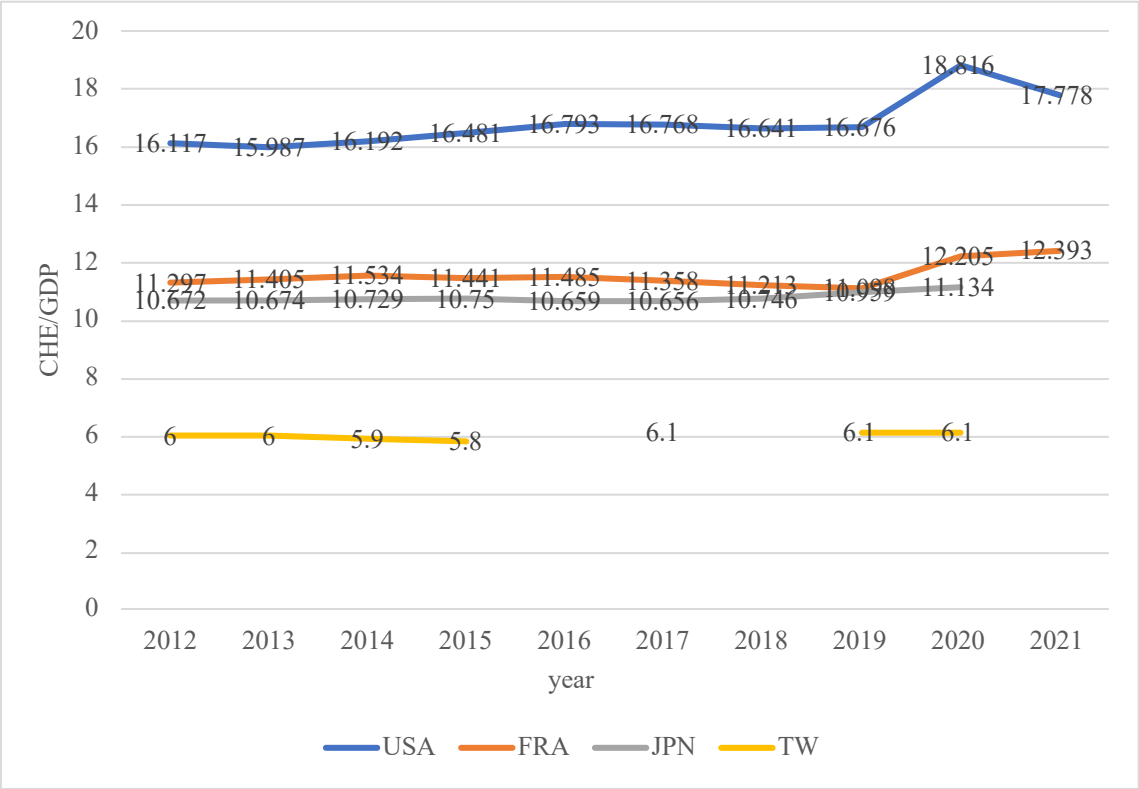

Figure 8. Current health expenditure per GDP in the United States, France, Japan, and Taiwan from 2012 to 2021 (16, 23).

(USA: United States, FRA: France, JPN: Japan, TW: Taiwan, CHE: Current health expenditure)

[13] https://www.oecd.org/

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Objective

The comparative analysis aims to provide valuable insights into the pharmaceutical industry's regulatory frameworks of drug access in different regions, emphasizing the need for ongoing research and policy development to decrease drug access delay globally. By analyzing two oncological medicines to show the different policy and drug access delay situations in the US, the EU, Japan, and Taiwan.

Method

Market authorization approval time is calculated from the initial submission date to the date of approval by the regulatory authorities in each country. The drug market authorization approval time data of the united states, the EU, and Japan from 2012 to 2021 can be reached from the R&D briefing report released by the Centre for Innovation in Regulatory Science (CIRS) located in London, UK, in 2022. The R&D briefing report published by the Centre for Innovation in Regulatory Science (CIRS) in London, UK, in 2022 shows the usage and the number of FRP. The reimbursement delay time of Taiwan and Japan can be extracted from Shih et al. (2020) plus the data from the report Shortening the Wait - patient access to Medicines in Europe on the EFPIA Homepage. The current health expenditure per GDP in the USA, France, and Japan from 2012 to 2021 can be taken from OECD, and Taiwan’s data can be extracted

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from the National health insurance annual statistical report published by the National Health Insurance Administration, Ministry of Health and Welfare.

After reviewing the different processes and policies in different countries on the topic of market authorization, pricing, and reimbursement, two case studies are analyzed to emphasize the results of my study. Regarding the case studies, the specific drug market authorization submission date is rarely disclosed by the authority. However, FDA may sometimes disclose it, and it sometimes can be disclosed by the report made by the pharmaceutical company itself. The drug authorization released date is always disclosed in the review report from FDA, the EPAR from EMA, and the interview form from PMDA and TFDA. The reimbursement submission and release date are not always disclosed. Sometimes the submission date can be retrieved from the Ameli[14] in France. The drug proposal will be included in the national health insurance benefit list from the Center For Drug Evaluation in Taiwan. The released date can be retrieved from the interview form of PMDA, Ameli from France, and the List of New Drug Items Listed in the National Health Insurance in Taiwan. The reimbursed price can be retrieved from Ameli in France, the NHI price list and information on generic drugs from the MHLW in Japan, and the online query service for health care medicines from the National Health Insurance Administration in Taiwan.

[14] https://www.ameli.fr/

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Case study

This report takes two oncological medicines as case studies, including Cyramza (Ramucirumab) and Zejula (Niraparib). Cancer is a leading death in both Eastern and Asian countries. Out of all the approvals granted between 2017 and 2021, the top five therapeutic areas accounted for 77% (821 out of 1060) of the total, including alimentary and metabolism, anti-infective, blood and blood forming organs, anti-cancer and immunomodulators, and nervous system. Within these top five therapeutic areas, anti-cancer and immunomodulator treatments comprised 53% (433) of the approvals. (30). Therefore, the delay of cancer drugs is lethal. It is crucial to analyze oncological drug access and affordability.

Cyramza (Ramucirumab) in gastric cancer

Based on the GLOBOCAN 2018 data, gastric cancer ranks as the third most fatal cancer globally, trailing behind lung and colorectal cancer. 1 out of 12 oncological lead death is contributed by gastric cancer. Over a million new cases happen yearly worldwide, with a 5.7% incidence rate among cancer. It is 2.2 times more common to see it happen to males than females in developed countries and 1.83 times in developing countries. The prevalence shows different geographically, is highest in East Asia (32.1 per 100,000 among males) than in North America (5.6 per 100,000) and North and East Africa (4.7 annual diagnoses per 100,000 males) (2, 31).

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CYRAMZA is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist. Angiogenesis happens when the tumor needs more nutrients by growing more blood vessels. CYRAMZA can suppress tumor angiogenesis and then suppress the tumor growth by lack of oxygen and nutrient. It can be treated in patients with advanced gastric disease and cancer of the gastroesophageal junction alone or with paclitaxel (another anticancer medicine) in adults whose disease progressed during or after chemotherapy was treated first (35).

Its ATC code of it is L01XC21. L stands for Antineoplastics and immunomodulators. L01X stands for Other antineoplastics, and XC stands for Monoclonal antibodies (8). Eli Lilly and Company produces it. Its valid license period for gastric cancer is from April 21, 2014, to April 21, 2024 in the US, December 19, 2014 to December 19, 2024 in the EU, March 2016 to March 2026 in Japan, and December 24, 2015 to December 24, 2025 in Taiwan (4, 7,13,14,18).

The time of receiving the market authorization in each country

To compare the market authorization waiting time of Cyramuza in each country, the data of the USA, the EU, Japan, and Taiwan from the letter from FDA, the European public assessment reports (EPAR) from EMA, interview form from PMDA and the data from TFDA are analyzed in Figure 9. It shows the time of receiving the market authorization in the USA, Japan, France, and Taiwan. The time of receiving the US

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market authorization from submission is 390 days (March 27, 2013- April 21, 2014) which is in priority review (4, 14). The time of receiving Japan's market authorization from submission is 270 days (July 2015 – March 2016) (18). The time of receiving EMA's market authorization from submission is 483 days (August 23, 2013- December 19, 2014) (7).

The date of receiving market authorization is December 24, 2015, in Taiwan, and TFDA does not disclose the submission date (13). The initial submission date in the US is faster than in the EU and in Japan and the market authorization waiting time in the US is 120 days longer than in Japan.

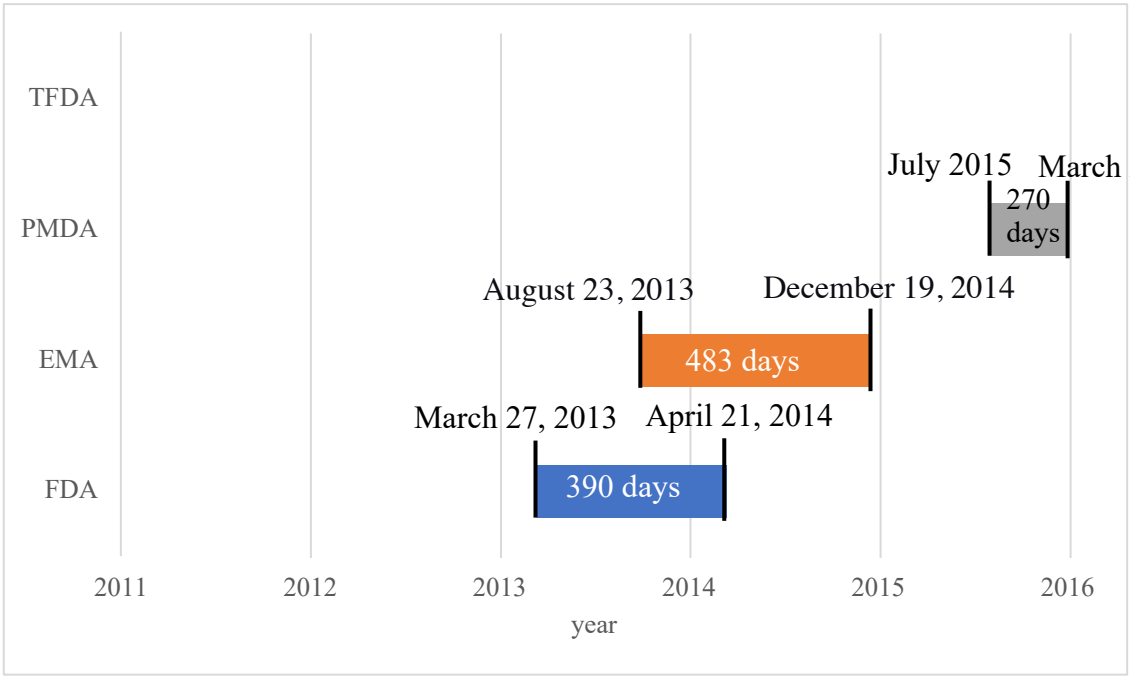

Figure 9. The time of receiving market authorization from submission in each country for Cyramza (4,7,13,14,18).

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The time of being on the reimbursed drug list after market authorization in each country

The time of being on the reimbursed drug list from submission in Taiwan since the market authorization date is 1963 days (December 16, 2015- May 1, 2021) (10, 12). To compare the reimbursed drug price in 2021 and 2023, the data from the Online query service for healthcare medicines from the National Health Insurance Administration in Taiwan is adapted into Table 3. Its reimbursed price is listed in Table 3, 9198 TWD (270 EUR) in 10 ml and 41,195 TWD (1,211 EUR) in 50 ml (10, 11).

Table 3. *The price of being on the reimbursed drug list from submission in Taiwan for Cyramza (11).*

Drug name	**Ingredient**	**Ingredient content**	**Specification quantity**	**Price (TWD)**	**Period**
CYRAMZA injection	Ramucirumab	10.000 MG/ML	10.0 ML	9292.00	May 1, 2021- March 31, 2023
CYRAMZA injection	Ramucirumab	10.000 MG/ML	10.0 ML	9198.00	April 1, 2023, until now
CYRAMZA injection	Ramucirumab	10.000 MG/ML	50.0 ML	41816.00	May 1, 2021- March 31, 2023

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CYRAMZA injection	Ramucirumab	10.000 MG/ML	50.0 ML	41195.00	April 1, 2023, until now

The time to be on the reimbursed drug list from submission in France is 1686 days (December 19, 2014- August 1, 2019); the authority decides the Medication will NOT be Reimbursable to National Insurance (9). The Committee takes note of the fact that the LILLY FRANCE laboratory is not requesting the inclusion of the proprietary medicinal product CYRAMZA 10 mg/mL (ramucirumab) in this indication and recalls that this medicinal product is therefore not reimbursable in the indication (8).

The time to be on the reimbursed drug list from submission in Japan is 55 days (March 26, 2015- May 20, 2015). The reimbursed prices of it are 76,659 JPY (515 EUR) for 10ml and 362,032 JPY (2,431 EUR) for 50 ml (27).

In order to compare the reimbursement waiting time of Cyramuza in each country, the reimbursement released date from the Ameli in France, and the Proposal for drugs to be included in the national health insurance benefit list from the Center for Drug Evaluation in Taiwan are combined in Figure 10. The reimbursement submission and release date are only sometimes disclosed. Figure 10 shows that the time of being on the reimbursed drug list after market authorization in France is shorter than in Taiwan, and its initial submission date before Taiwan and Japan.

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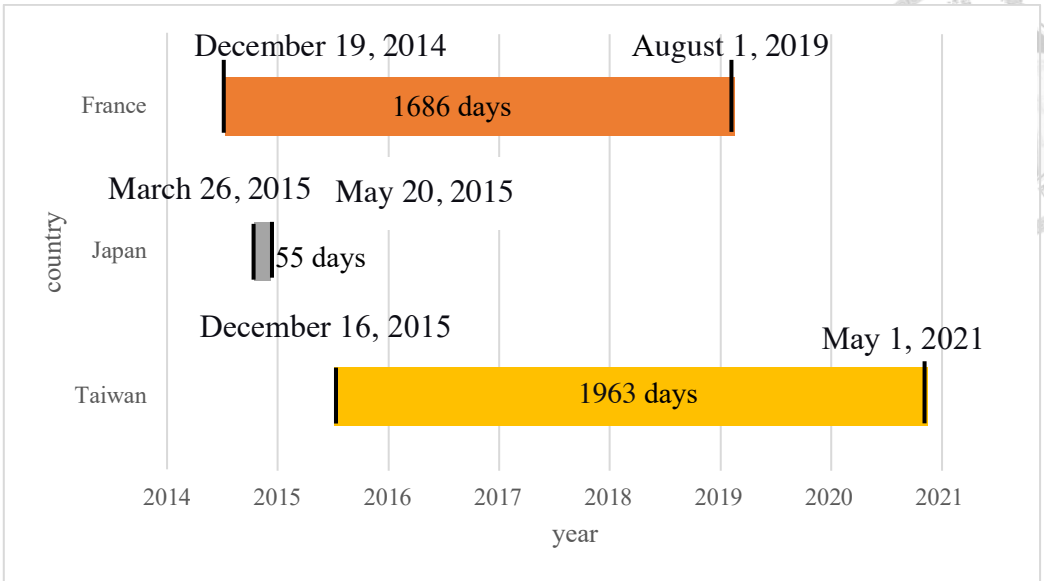

Figure 10. The time of being on the reimbursed drug list after market authorization in each country for Cyramza (8-12).

Zejula (Niraparib) in ovarian cancer

Ovarian cancer is the seventh most common cancer and the fifth high cancer-related death among women. White woman has the highest prevalence (11.3 out of every 100,000 women), followed by Hispanics, Asian/Pacific Islander, African Americans, and American Indian/Alaska natives. The risk may occur more with increasing age. Occurrence happens after 50 years old, and the average diagnosis age is between 50 to 70 years old (37).

Zejula is a PARP inhibitor blocking PARP-1 and PARP-2. PARP is the enzyme that can repair the DNA damage on cancer cells during its cell division. Blocking the enzyme on the tumor can cause tumor death. It can be treated for a patient who is newly diagnosed or recurrent in the disease and has a complete response or partial response

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after the platinum-based medicine (41).

The ATC code is L01XX54, and the producer is GlaxoSmithKline (Ireland) Limited (41). Takeda had a license agreement for sales in Taiwan and Japan with GlaxoSmithKline (Ireland) Limited. Its valid license period for ovarian cancer is from March 27, 2017, to March 27, 2027 in the US, November 16, 2017 to November 16, 2027 in the EU, September 2020 to September 2030 in Japan, and January 13, 2021 to January 13, 2031 in Taiwan (19, 26, 41, 42)

The time of receiving the market authorization in each country

In order to compare the market authorization waiting time of Zejula in each country, the data of the USA, the EU, Japan, and Taiwan from the letter from FDA, the EPAR from EMA, interview form from PMDA and the data from TFDA, are analyzed in Figure 11. It shows the time of receiving the market authorization in the USA, Japan, France, and Taiwan. The time of receiving the US market authorization from submission is 696 days (May 2015- March 27, 2017) which is under priority review (42). The time of receiving Japan's market authorization from submission is 640 days (December 2018 – September 2020) (19). The time of receiving EMA's market authorization from submission is 408 days (October 4, 2016 - November 16, 2017) (41).

The date of receiving market authorization is January 13, 2021 in Taiwan, and the submission date is not disclosed by TFDA (26). Its initial submission date in the US is

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faster than the one in EU and in Japan. The result shows the market authorization waiting time in the US is 56 days longer than Japan. And the market authorization waiting time are longer than the mean waiting time shown in figure 2.

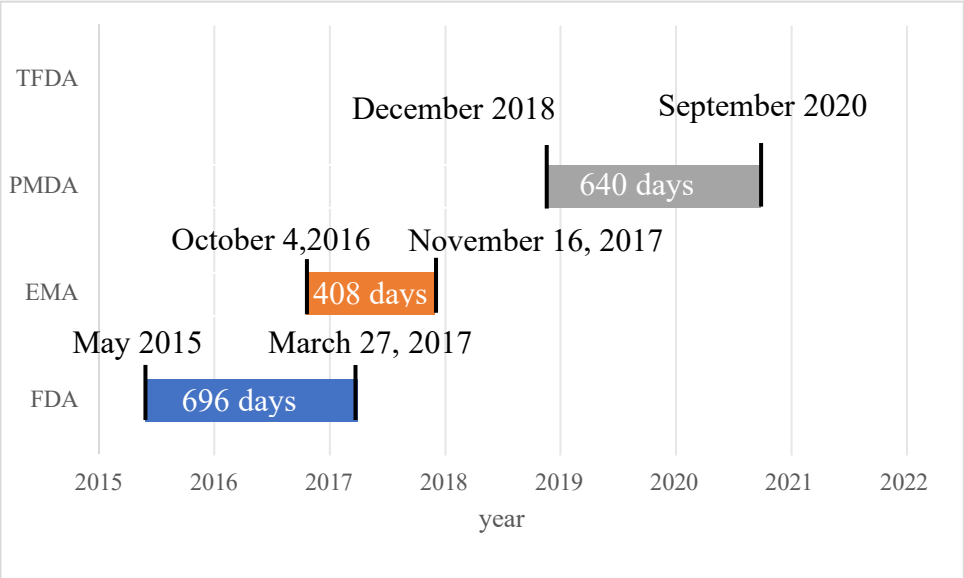

Figure 11. The time of receiving market authorization from submission in each country for Zejula (19, 26, 41, 42).

The time of being on the reimbursed drug list after market authorization in each country

The time of being in the reimbursed drug list from submission in Taiwan since the market authorization date is 718 days (January 13, 2021- January 1, 2023). Its reimbursed price is 2459 TWD (72.93 EUR) in 1 Niraparib 100mg capsule (40).

The time of being in the reimbursed drug list from submission in France since the market authorization date is 723 days (November 16, 2017- November 9, 2019). The reimbursed price is 82.1 EUR for 1 Niraparib 100mg capsule (43).

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The time of being in the reimbursed drug list from submission in Japan since the market authorization date is 58 days (September 25, 2020- November 18, 2020). Its reimbursed prices are 10,370.20 JPY (69.71 EUR) in 1 Niraparib 100mg capsule (27).

In order to compare the reimbursement waiting time of Zejula in each country, the reimbursement released date from the Ameli in France, and the Proposal for drugs to be included in the national health insurance benefit list from the Center for Drug Evaluation in Taiwan, are analyzed in figure 12. It shows that the time of being on the reimbursed drug list after market authorization in France is longer than in Taiwan and Japan, and its initial submission date is prior to Taiwan and Japan.

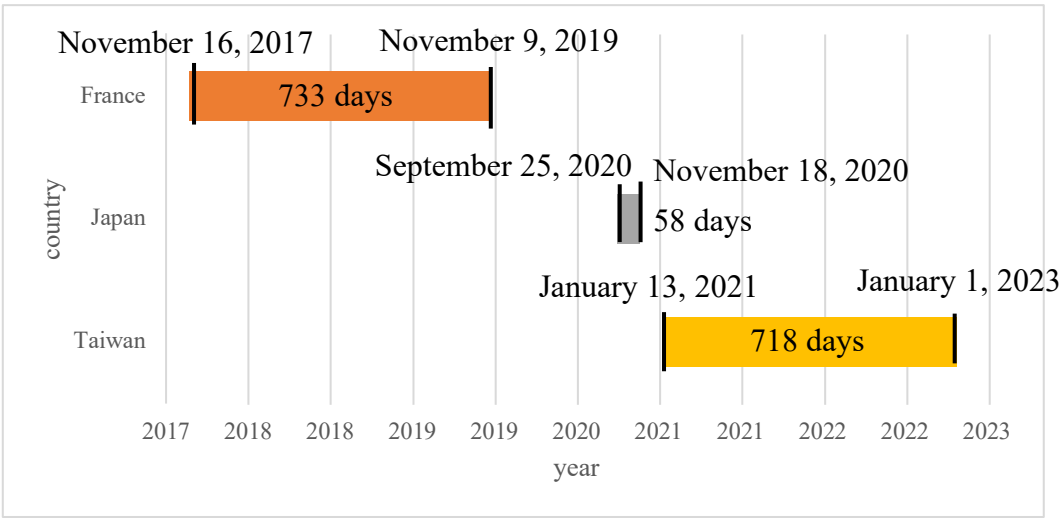

Figure 12. The time of being on the reimbursed drug list after market authorization in each country for Zejula (27, 40, 43).

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Discussion

The result shows that the market authorization waiting time is usually shorter in FDA (median: 285.4 days) than in PMDA (median: 312.3 days), TFDA (median: 328.6 days), and EMA (median: 435.6 days) (Figure 2). And the drug market authorization is usually submitted to FDA and EMA first. The market authorization delay in case studies can only be calculated in FDA, EMA, and PMDA because TFDA doesn't disclose the submission date. Both case studies are only under priority review in FDA but not in PMDA, EMA, and TFDA. Although they are under priority review by FDA, the review period is 105 days and 411 days longer than the median waiting time of the FDA in Cyramza and Zejula. The case studies show that market authorization delay in the US is more severe than in the EU and Japan. It is uncommon to see the market authorization waiting time in the US longer than in Japan. It is probably because of the lack of a master file of safety and efficacy data.

In the pricing and reimbursement process, Japan is the fastest decision maker with a mean of 69 days waiting only, followed by Italy, Taiwan, France, and Spain, respectively, with a mean of 436 days, 458 days, 508 days, and 629 days. In a case study of Cyramza (Ramucirumab), the waiting time for being reimbursed is 1963 days (1455 days delay) in France and 1686 days (1228 delays) in Taiwan. It is worth to mention the incidence of gastric cancer is higher in the Asian population than in the

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white people, reimbursement should happen longer in Taiwan than in France for careful evaluation in budget consideration, but it is not. In the case study of Zejula (Niraparib), It is 733 days (225 days delay) in France and 718 days (260 days delay) in Taiwan. The incidence of ovarian cancer is higher in the white population than the Asian population, reimbursement should occur longer in France than in Taiwan, and it shows the right trend. Japan's reimbursement process is usually on time. It should only wait 60-90 days after market authorization because there is a law to maintain the waiting time. Typically, the waiting time in France and Taiwan should be similar, but in the case studies, they do not all show the same trend. The report finds that the reimbursement delay can vary significantly because of the health care budget and local unmet medical need differences.

In the market authorization process, each country has already implemented more and more FRPs, including «Priority Review», «Accelerated Approval», «Fast Track», and "Breakthrough Therapy» in the US, «EMA Accelerated Assessment", «EMA Conditional Approval», «EMA Exceptional Circumstances», and «EMA PRIME» in the EU, «PMDA Priority Review», «PMDA Conditional Early Approval», and «PMDA Sakigake (pioneer)» in Japan, and «Abbreviated Review», «Priority Review», «Accelerated Approval», «Breakthrough Therapy», and «Pediatric and Rare Severe Disease Priority Review Voucher Program» in Taiwan, for the new drug launch on the

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local market. The waiting time is gradually similar. However, FDA and EMA are the first two authorities for drug market authorization. Asian countries are always later than those. One strategy to expedite market authorization in Japan is to accelerate bridging studies. This can be achieved by optimizing pharmaceutical regulations and technologies, initiating bridging studies early in the drug development process, actively participating in global research and development (R&D) trials, and considering the inclusion of pre-defined windows within global trials to meet Japanese registration requirements (39).

The reimbursement process delay in each countries varies a lot because of the Pharmacoeconomics difference. The marketing authorization in Asian countries always starts later than FDA and EMA. Therefore, Asian countries should reduce the reimbursement submission delay to avoid drug access delays. Japan implements the reimbursement delay should be within 60-90 days, which is a good standard for other Asian countries to follow. All the regulatory authorities should disclose drug access-related data for better research by the researchers. Moreover, Taiwan's current health expenditure per GDP is the lowest compared to the United States, France, and Japan. Taiwan's government might increase the budget for the patient to access the lower price drugs and decrease the reimbursement release waiting time, increasing the number of innovative medicines coming into the local market.

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Conclusion

The comparative analysis aims to provide valuable insights into the pharmaceutical industry's regulatory frameworks of drug access in different regions, emphasizing the need for ongoing research and policy development to decrease drug access delay globally.

This report takes two molecules (Cyramza (Ramucirumab) and Zejula (Niraparib)) to emphasize some key findings. North America, Europe, and Asia are implementing more facilitated regulatory pathways in the market authorization process so that the market authorization waiting times are similar. But the start date of market authorization in Asian countries is always slower than in the US and the EU. Moreover, the drug reimbursement waiting time differs in each country because of the differences in health care budget and local unmet medical needs.

One strategy to expedite market authorization in Japan is to accelerate bridging studies. This can be achieved by optimizing pharmaceutical regulations and technologies, initiating bridging studies early in the drug development process, actively participating in global research and development (R&D) trials, and considering the inclusion of pre-defined windows within global trials to meet Japanese registration requirements. Moreover, FDA and EMA are the first two authorities for drug market authorization. Asian countries are always later than those. Therefore, Asian countries

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should reduce the reimbursement submission delay to avoid drug access delays. Japan implements the reimbursement delay should be within 60-90 days, which is a good standard for other Asian countries to follow. All the regulatory authorities should disclose drug access-related data for better research by the researchers. Taiwan's current health expenditure per GDP is the lowest compared to the United States, France, and Japan. Taiwan's government must increase the budget for the patient to access the lower price drugs, decrease the reimbursement release waiting time, and increase the number of innovative medicines coming into the local market.

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Abbreviation list

A10 reference countries: the United States, the United Kingdom, Canada, France, Belgium, Germany, Japan, Sweden, Australia, and Switzerland,

ATU: Autorisation Temporaire d'Utilisation (temporary use authorizations)

ASMR: anterior superiormedial protocerebrum (Authority of Health Scale)

ATC: Anatomical Therapeutic Chemical classification

CIRS: Centre for Innovation in Regulatory Science

CHE: Current health expenditure

CEPS: Comité économique des produits de santé (Economic Committee for Health Products)

CT: Transparency Committee

CEESP: Commission Evaluation Economique et de Santé Publique (The Economic and Public Health Assessment Committee)

DBC: Drug Benefit Committee

EFPIA: European Federation of Pharmaceutical Industries and Associations

EPAR: European public assessment report

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

FRP: facilitated regulatory pathways

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GDP: Gross Domestic Product

HTA: Health technology assessment

HAS: Haute Autorité de santé (French National Authority for Health)

MHLW: Ministry of Health, Labour and Welfare

MOHW: Minister of Health and Welfare

NDA: New Drug Application

NAS: New active substance

NHIA: National Health Insurance Administration

NHI: National health insurance

OECD: Organization for Economic Co-operation and Development

PBRS: Pharmaceutical Benefit and Reimbursement Scheme

PARP: poly ADP ribose polymerase

PMDA: Pharmaceuticals and Medical Devices Agency

R&D: Research and development

SMR: Service Médical Rendu (actual benefit)

TFDA: Taiwan Food and Drug Administration

UNCAM: Union Nationale des Caisses d'Assurance Maladie (National Union of Health Insurance Funds)

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